

Expert Opinion

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An update on the pharmacological treatment of obsessive-compulsive disorder

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The purpose of this article is to introduce the reader to an updated evidence-based drug treatment algorithm to be employed in patients with obsessive-compulsive disorder (OCD). Relevant studies were identified through a comprehensive review and classified according to the type of patients enrolled, the quality of the study design and the invasiveness availability, and complexity of the therapeutic approach. When ineffective, therapeutic trials with first-line strategies (such as the selective serotonin re-uptake inhibitors [SSRIs] and venlafaxine) or cognitive-behavioral therapy should be followed by treatment approaches such as clomipramine, augmentation with antipsychotics or pindolol, or SSRI megadoses. These therapeutic strategies are expected to help most patients with OCD. Additional approaches include intravenous clomipramine, oral morphine, 'heroic drug strategies', deep brain stimulation and functional neurosurgery. Independent studies are urgently needed to help identify the most promising drug treatment sequences for OCD.

Keywords: obsessive-compulsive disorder, serotonin re-uptake inhibitors

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1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by the presence of recurrent, persistent and unwanted thoughts, impulses or images (obsessions) that the person attempts to ignore, suppress or to neutralize with some other thought or action, and by repetitive behaviors (e.g., hand washing, ordering or checking) or mental acts (e.g., praying, counting or repeating words silently) that the person feels driven to perform in response to an obsession or according to rules that must be applied rigidly (compulsions). To meet diagnostic criteria for OCD, a patient must display either obsessions or compulsions that result in marked anxiety or distress, are time consuming (take more than 1 h a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning or usual social activities or relationships [1].

According to epidemiological studies that employed the Composite International Diagnostic Instrument (CIDI) as a diagnostic instrument, although the 1-month prevalence of OCD ranges from 0.3 to 3.1% of the general population [2], the 1-year incidence is ~ 0.2% [3]. It has been argued that such discrepancy may stem from factors such as the varying levels of technical skills of the interviewers (mental health professionals versus lay personnel), the different settings of evaluation (interviews conducted personally versus interviews by telephone), the increasing use of technological aids such as computer-assisted assessments, and finally, the intrinsic characteristics of the population under study.

Epidemiological inconsistencies aside, it is clear that a significant number of individuals in the community suffer from OCD. When these individuals decide to search for professional assistance and to become patients, it is often the case that their OCD has reached substantial levels of severity [4], making their correct diagnosis and prompt treatment of utmost importance.

A number of recent and important reviews suggested that selective serotonin re-uptake inhibitors (SSRIs) employed in the maximum-tolerated doses for at least 10 – 12 weeks should be considered the first-line treatment strategy for OCD [5,6]. In fact, despite this evidence-based consensus among experts, the basic psychiatric care of OCD continues to be an area with considerable room for improvement.

For example, Blanco *et al.* analyzed the physician-reported data from the 1997 and 1999 American Psychiatric Institute for Research and Education (APIRE) Practice Research Network Study of Psychiatric Patients and Treatments and described demographic, clinical and treatment characteristics of 123 patients with a diagnosis of OCD being medicated by a nationally representative sample of North American psychiatrists [7].

According to Blanco *et al.*, only 39.4% of the sample patients received an SRI at a dose thought to be most effective for OCD, or were having their dose titrated upward [7]. Prescription of benzodiazepines or antipsychotics was common among these patients, often without the concomitant use of an SRI. Similar findings, suggesting that OCD treatment in clinical practice often departs from evidence-based care, were also reported in other parts of the US [8,9] and in Holland [10].

It is possible that a wider dissemination of practice guidelines would increase the provision of appropriate treatment for patients with OCD [7]. However, even in the case that most psychiatrists start prescribing updated evidence-based, first-line pharmacological treatment for OCD (i.e., high-dose serotonin re-uptake inhibitor [SRI] for at least 10 – 12 weeks), 40 – 60% of patients would still not show a positive response to this treatment approach. Although the definition of response has varied considerably [11], there is an urgent need to provide clinicians with information that would help them decide which treatment sequence would best suit patient needs.

The objective of this review is twofold. The first aim is to provide mental health professionals, especially psychiatrists, with an update on the safest and most effective pharmacological treatment strategies available for patients with OCD. The second aim is to introduce the reader to a flexible, evidence-based treatment algorithm that may be employed in 'real-life' situations, whenever clinicians face treatment-resistant or refractory OCD (Figure 1).

Articles were retrieved from the the PubMed electronic bibliographic database using the following combination of medical subject heading (MeSH) terms: obsessive-compulsive disorder (MeSH terms) AND (double-blind study [MeSH Terms] OR drug therapy [MeSH Terms] OR therapeutics [MeSH Terms] OR meta-analysis [MeSH Terms]). The

search strategy was restricted by the limits function available on the PubMed (i.e., only studies in English, German, French or Spanish were selected). The reference lists of the articles identified through these methods were further explored. Book chapters on the pharmacotherapy of OCD, their references as well as scientific symposia records, were also reviewed.

Selected studies were classified according to the following features: i) type of patients enrolled in the treatment trial (i.e., drug-free or treatment-resistant OCD); ii) invasiveness of the therapeutic approach: reduced (oral drugs without abuse potential), moderate (intravenous or oral drugs with abuse, tolerance and withdrawal reactions potential) or increased invasiveness (surgical or non-surgical approaches involving anesthetic procedures, such as electroconvulsive therapy [ECT], deep brain stimulation or neurosurgery); iii) design of the study (controlled studies or other studies with less sophisticated treatment designs); iv) availability of the therapeutic approach: widespread (oral drugs or electroconvulsive treatment) or restricted availability (i.e., therapeutic approaches that are only offered in specialized or academic centers, such as deep-brain stimulation or neurosurgery); and v) treatment complexity (i.e., treatments with reduced [oral or intravenous drugs], moderate ['heroic drugs strategies', ECT and transcranial magnetic stimulation (TMS)] or high [only performed by specialized personnel, for example deep brain stimulation and neurosurgery] complexity).

Each type of treatment was allocated in the corresponding level of the decision tree devised by the authors according to the above-mentioned characteristics (Table 1). Preference was given to treatment approaches with reduced invasiveness, efficacy demonstrated by controlled trials, widespread availability and reduced complexity of administration. The more a given treatment approach displayed these features, the closer it was to the initial levels of our decision tree (see Table 1). Open studies suggesting the efficacy of a particular drug that were later followed by controlled studies (either with positive or negative outcomes) were preliminarily discarded from this review.

The first author screened a total of 1236 studies available on PubMed. Additional studies were also selected by means of alternative search strategies. Selected articles included not only treatment trials, but also key meta-analytical [12-20], systematic [5,6,21] and narrative reviews [22-24], as well as treatment guidelines and recommendations from several different professional societies, including the Canadian Psychiatric Association [25], the British Association of Psychopharmacology [26], the World Council of Anxiety [27], the World Federation of Societies of Biological Psychiatry [28] and the Expert Consensus Panel for Obsessive-Compulsive Disorder [29].

The drugs identified in this review and their corresponding highest level of evidence (i.e., the evidence generated by the most sophisticated studies that tested them) are depicted in Tables 2 (drug-free OCD) and 3 (treatment-resistant OCD).

Other biological treatments, including ECT, TMS, DBS and functional neurosurgery, along with the highest-level

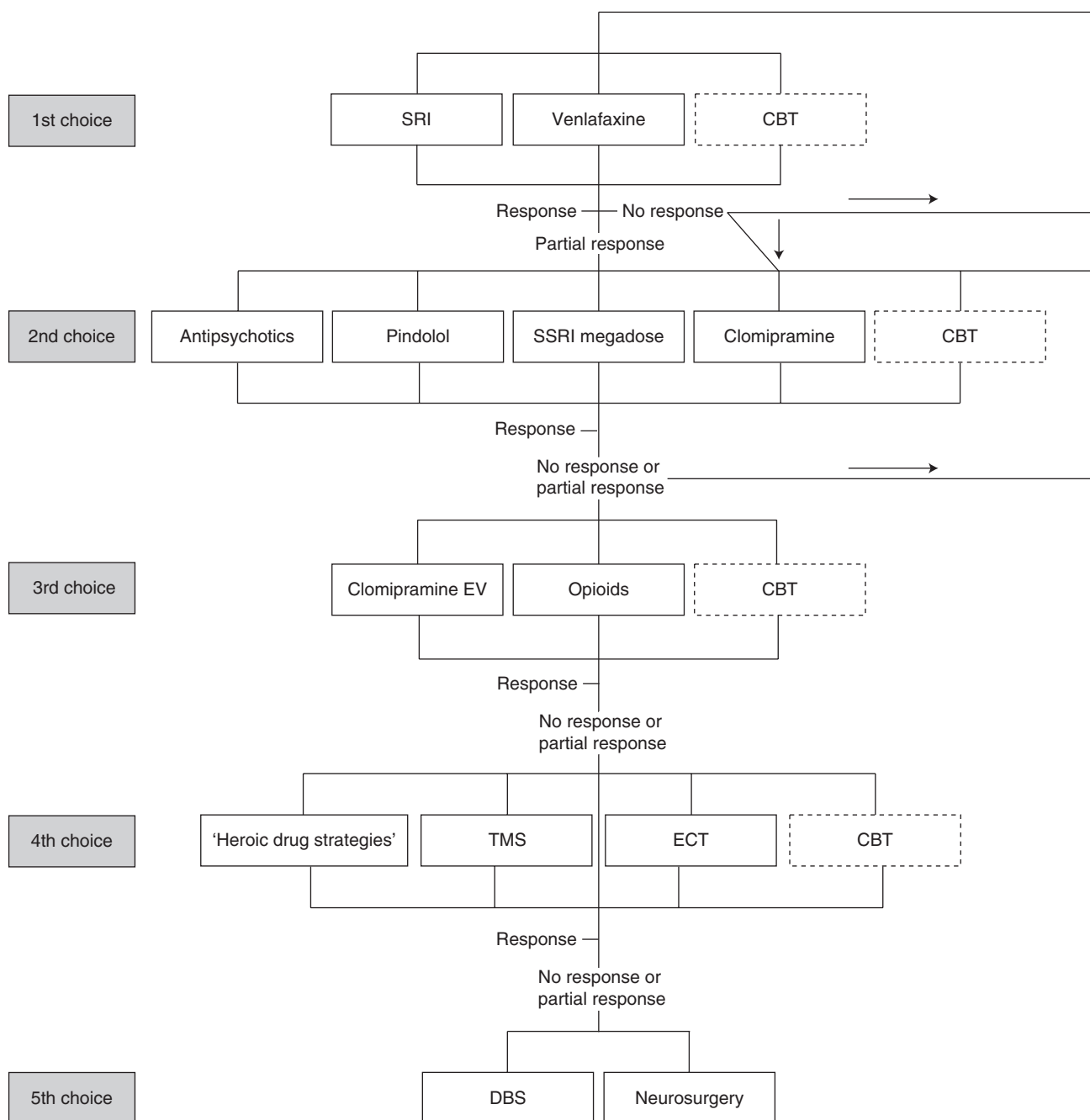


Figure 1. Treatment algorithm for patients with obsessive-compulsive disorder.

'Heroic drug strategies': non-tested 'off-label' drug combinations including SSRI, clomipramine or venlafaxine plus drugs targeted to dopaminergic (e.g., amisulpride), serotonergic (e.g., clomipramine, triptophan, triptans, fenfluramine, and perospirone), noradrenergic (e.g., reboxetine), glutamatergic (e.g., riluzole, memantine, lamotrigine and topiramate), GABAergic (e.g., valproate) and nicotinic receptors (e.g., nicotine gum) and ion channels (e.g., carbamazepine and oxcarbazepine).

Given its undisputable effectiveness in the treatment of OCD, CBT as a therapeutic option was also included in this treatment algorithm. Nevertheless, as this review is primarily concerned with the biological treatments of OCD, CBT was included in dashed boxes.

Antipsychotics: primarily haloperidol and risperidone.

SSRI megadose: primarily sertraline.

Opioids: Primarily oral morphine;

CBT: Cognitive-behavioral therapy; DBS: Deep brain stimulation; ECT: Electroconvulsive therapy; SSRI: Selective serotonin re-uptake inhibitors; TMS: Transcranial magnetic stimulation.

Table 1. Differential features of each treatment stage.

Treatment features	First choice	Second choice	Third choice	Fourth choice	Fifth choice
Type of patient	Drug free	Treatment resistant	Treatment resistant	Treatment resistant	Treatment resistant
Treatment invasiveness	Reduced	Reduced	Moderate	Moderate for some*	Increased
Type of study	Controlled	Controlled	Controlled	Controlled for some [‡]	Controlled for some [¶]
Availability	Widespread	Widespread	Widespread	Widespread for some [§]	Restricted
Complexity	Reduced	Reduced	Reduced	Moderate for some*	Increased

*Electroconvulsive therapy; [‡]Transcranial magnetic stimulation; [§]Heroic drug strategies; [¶]Deep brain stimulation.

trials that have assessed them, are listed in Table 4. Based on the information gathered through these investigative strategies, a treatment algorithm was proposed (Figure 1).

2. First-line treatments

First-choice treatments comprised those approaches with efficacy demonstrated by controlled trials, minor invasiveness, widespread availability and minimal complexity of administration. Certainly, as noted in most recent reviews and expert guidelines on the issue of pharmacological treatment of OCD, SSRIs fulfil all of these criteria. At present, there are several double-blind, placebo-controlled studies showing positive results with fluvoxamine [30-33], fluoxetine [34,35], sertraline [36-38], paroxetine [39-41], citalopram [42] and, more recently, escitalopram [43]. All SSRIs (as well as clomipramine) have been approved for use in adults with OCD by the FDA, with the exception of the newer citalopram and escitalopram. Although some of these drugs were not tested in a controlled, fixed-dose method to assess optimal doses (e.g., fluvoxamine), most studies with SSRIs indicate that patients should be treated with the maximum tolerated doses for at least 12 weeks. However, there is some evidence that additional improvements may occur even later, and a number of guidelines recommend the continuation of treatment for at least 1 to 2 years [23,27,29].

Given the ever-increasing number of studies demonstrating the efficacy of different SSRIs in the treatment of OCD, it is natural to ask which of them is associated with a greater magnitude of effect. Unfortunately, there is a scarcity of head-to-head comparison studies between such drugs, and only findings from the meta-analytic reviews of placebo-controlled studies can be relied on [13-16]. These meta-analyses suggest that there are no significant differences between SSRIs in terms of efficacy. Nevertheless, as they differ in terms of tolerability profile, the clinician may opt for a particular drug instead of others.

Some recent studies have investigated whether adding a second drug (such as mirtazapine) to an SSRI from the outset of treatment would result in additional symptom improvement in patients with OCD. For example, in a single-blind, 12-week

clinical trial with citalopram (20–80 mg/day) plus mirtazapine (15–30 mg/day) or citalopram plus placebo, Pallanti *et al.* reported that the combined treatment group exhibited an earlier onset of response and an attenuation of some undesired side effects found in the group treated only with citalopram [44]. Nevertheless, no difference between these approaches emerged at the end of the weeks 8 and 12 of treatment.

Other studies with different drugs were performed with similar goals, but some serious methodological limitations hampered the interpretation of their results. For example, Crockett *et al.* performed a double-blind, randomized, parallel-controlled comparison of clonazepam (mean dose of 2.7 mg/day) versus placebo in combination with sertraline (mean dose of 95.6 mg/day) in OCD [45]. Although the combination did not bring greater benefit regarding the OCD symptoms, 48% of the patients failed to complete treatment, and the influence of this high dropout rate complicates the interpretation of these results. However, the authors of the present article have found a small subset of patients with OCD and comorbid panic disorder in which the prescription of clonazepam, either alone or combined with low-dose non-SSRI antidepressants, was associated with impressive rates of remission of the OCD symptoms [46]. Nevertheless, if clonazepam is an effective first-line treatment for OCD, its optimal dose and the corresponding treatment-responsive OCD phenotype remains to be established in future controlled trials.

In an 8-week, double-blind, placebo-controlled study conducted by Noorbala *et al.*, 15 subjects were randomly assigned to clomipramine (150 mg/day) plus nortriptyline (50 mg/day) and 15 patients to clomipramine (150 mg/day) plus placebo [47]. The authors found a significant reduction in the scores of Yale-Brown Obsessive compulsive scale (Y-BOCS) at as early as 2 weeks of treatment in the combined group, compared with clomipramine alone. However, it is unclear how the combined group would perform if a third group treated with 200 mg/day of clomipramine had been included for the sake of comparison.

Although a number of case reports, case series and active-comparison studies have suggested that venlafaxine, a serotonin and noradrenaline re-uptake inhibitor (SNRI), might help patients with OCD, the only published

Table 2. The highest level of evidence available for different drug treatments in drug-free OCD.

	Number of favorable studies	Number of unfavorable studies	Invasiveness	Availability	Complexity	Comments
SSRIs						
Fluvoxamine	11 RCTs [30-33,124-130]	–	Reduced	Widespread	Reduced	First-line treatment
Fluoxetine	4 RCTs [34,35,119,131]	–	Reduced	Widespread	Reduced	First-line treatment
Sertraline	4 RCTs [36,37,132,133]	1 RCT [38]	Reduced	Widespread	Reduced	First-line treatment
Paroxetine	4 RCTs [39-41,134]	–	Reduced	Widespread	Reduced	First-line treatment
Citalopram	1 RCT [42]	–	Reduced	Widespread	Reduced	First-line treatment
Escitalopram	1 RCT [43]	–	Reduced	Widespread	Reduced	First-line treatment
Zimelidine	1 RCT [135]	–	Reduced	Withdrawn	Reduced	Not recommended
SNRIs						
Venlafaxine	2 RCTs [134,136,137]	1 RCT [37]	Reduced	Widespread	Reduced	Potential first-line treatment
PO clomipramine	21 RCTs [39,119,126-129,131,133,136,138-148]	–	Reduced	Widespread	Reduced	Second-line treatment due to side effects
IV clomipramine	1 RCT [55]	–	Reduced	Widespread	Reduced	Not recommended for drug-free patients
NaSSAs						
Mirtazapine	1 RCT [44]	–	Reduced	Widespread	Reduced	Potential first-line treatment with SSRIs, may accelerate response to SSRIs
NRIs						
Bupropion	–	1 OS [149]	Reduced	Widespread	Reduced	Not recommended, may worsen OCD
MAOIs						
Phenelzine	1 RCT [150]	1 RCT [151]	Reduced	Widespread	Moderate	Not recommended, although it may help patients with symmetry obsessions
Clorgiline	–	1 RCT [152]	Reduced	Widespread	Moderate	Not recommended
Tranylcipromine	2 OS [153,154]	–	Reduced	Widespread	Moderate	Not recommended, although it may help patients with severe anxiety
Tricyclics						
Amiritypyline	–	1 RCT [155]	Reduced	Widespread	Reduced	Not recommended
Imipramine	–	1 RCT [156]	Reduced	Widespread	Reduced	Not recommended, although it may be a low-cost alternative
Desipramine	–	2 RCTs [157,158]	Reduced	Widespread	Reduced	Not recommended

5-HT: Serotonin; CR: Case report; MAOI: Monoamine oxidase inhibitor; NaSSA: Noradrenaline and specific serotonergic drug; NRI: Noradrenaline re-uptake inhibitor; OCD: Obsessive-compulsive disorder; OS: Open study; RCT: Randomized controlled trial; SNRI: Serotonin and noradrenaline re-uptake inhibitor; SSRI: Selective serotonin re-uptake inhibitor.

Table 2. The highest level of evidence available for different drug treatments in drug-free OCD.

	Number of favorable studies	Number of unfavorable studies	Invasiveness	Availability	Complexity	Comments
Nortriptyline	1 RCT [159]	–	Reduced	Widespread	Reduced	Potential first-line treatment with SSRIs, may accelerate response
5-HT modulators						
Trazodone	–	1 RCT [160]	Reduced	Widespread	Reduced	Not recommended.
Ondasetron	1 OS [161]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Buspirone	1 RCT [162]	–	Reduced	Widespread	Reduced	Not recommended, study with questionable response criteria and treatment duration (6 weeks)
Second messengers						
Inositol	1 RCT [163]	–	Reduced	Widespread	Reduced	Not recommended
Benzodiazepines						
Clonazepam	1 RCT [164]	2 RCTs [165,166]	Reduced	Widespread	Reduced	Not recommended, although it may help severe anxiety-related OCD
Alprazolam	–	1 OS [167]	Reduced	Widespread	Reduced	Not recommended
Herbal treatments						
St John's Wort	–	1 RCT [168]	Reduced	Widespread	Reduced	Not recommended
Mood stabilizers						
Lithium	–	2 RCTs [169,170]	Reduced	Widespread	Reduced	Not recommended
Carbamazepine	1 OS [171]	2 OS [172,173]	Reduced	Widespread	Reduced	Not recommended, although it may help epilepsy-related OCD
Antipsychotics						
Aripipazole	1 OS [174]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Hormonal treatments						
Flutamide	–	1 OS [175]	Reduced	Widespread	Moderate	Not recommended
Ocytocin	–	1 RCT [176]	Reduced	Widespread	Reduced	Not recommended

5-HT: Serotonin; CR: Case report; MAOI: Monoamine oxidase inhibitor; NaSSA: Noradrenaline and specific serotonergic drug; NRI: Noradrenaline re-uptake inhibitor; OCD: Obsessive-compulsive disorder; OS: Open study; RCT: Randomized controlled trial; SNRI: Serotonin and noradrenaline re-uptake inhibitor; SSRI: Selective serotonin re-uptake inhibitor.

Table 3. The highest level of evidence available for different drug treatments in treatment resistant OCD.

	Number of favorable studies	Number of unfavorable studies	Invasiveness	Availability	Complexity	Stage
Antipsychotics						
Haloperidol	1 RCT [177]	–	Reduced	Widespread	Reduced	Second-line treatment
Risperidone	3 RCTs [178-180]	–	Reduced	Widespread	Reduced	Second-line treatment
Olanzapine	1 RCT [181]	1 RCT [182]	Reduced	Widespread	Reduced	Second-line treatment
Quetiapine	2 RCTs [183,184]	2 RCTs [185,186]	Reduced	Widespread	Reduced	Second-line treatment
Amisulpiride	1 OS [187]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Perospirone	1 OS [62]	–	Reduced	Unavailable	Reduced	Not recommended until further studies are available
Serotonergic drugs						
Oral clomipramine	2 RCTs [119,188]	–	Reduced	Widespread	Reduced	Second-line treatment
Intravenous clomipramine	2 RCTs [53,56]	–	Moderate	Widespread	Reduced	Third-line treatment
Oral citalopram	1 RCT [188]	–	Reduced	Widespread	Reduced	Second-line treatment
Intravenous citalopram	1 OS [189]	–	Moderate	Reduced	Reduced	Not recommended due to low availability
Triptophan	1 OS [59]	–	Moderate	Widespread	Reduced	Fourth-line treatment
Sumatriptan	2 CRs [60,190]	–	Moderate	Widespread	Reduced	Fourth-line treatment
Fenfluramine	3 OS [61,191,192]	–	Reduced	Withdrawn	Reduced	Not recommended due to cardiac side effects and low availability
Pindolol	1 RCT [193]	1 RCT [194]	Moderate	Widespread	Reduced	Second-line treatment
Buspirone	–	3 RCTs [195-197]	Moderate	Widespread	Reduced	Not recommended
Noradrenergic drugs						
Amitriptyline	–	1 RCT [155]	Reduced	Widespread	Reduced	Not recommended
Desipramine	–	1 RCT [198]	Reduced	Widespread	Reduced	Not recommended
Reboxetine	1 CR [63]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Venlafaxine	1 RCT [137]	–	Reduced	Widespread	Reduced	Second-line treatment
Glutamatergic drugs						
Riluzole	1 OS [64]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Memantine	2 CRs [66,67]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Lamotrigine	–	1 OS [68]	Reduced	Widespread	Reduced	Fourth-line treatment

CR: Case report; OCD: Obsessive compulsive disorder; OS: Open study; RCT: Randomized, controlled trial.

Table 3. The highest level of evidence available for different drug treatments in treatment resistant OCD.

	Number of favorable studies	Number of unfavorable studies	Invasiveness	Availability	Complexity	Stage
Topiramate	2 OS [70,199]	–	Reduced	Widespread	Reduced	Fourth-line treatment
GABAergic drugs						
Valproate	2 CRs [71,200]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Nicotinic drug						
Nicotine gum	1 OS [72]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Ion-channels drugs						
Carbamazepine	1 CR [74]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Oxcarbazepine	1 CR [76]	–	Reduced	Widespread	Reduced	Fourth-line treatment
Opioid drugs						
Morphine	1 RCT [201]	–	Reduced	Restricted	Moderate	Third-line treatment
Alkali metals						
Lithium	–	2 RCTs [202,203]	Reduced	Widespread	Reduced	Not recommended
Second messengers						
Inositol	–	1 RCT [204]	Reduced	Widespread	Reduced	Not recommended
Nutritional supplements						
ω-3 fatty acids	–	1 RCT [205]	Reduced	Widespread	Reduced	Not recommended
Hormonal treatments						
Thyroxine	–	1 RCT [206]	Reduced	Widespread	Reduced	Not recommended

CR: Case report; OCD: Obsessive compulsive disorder; OS: Open study; RCT: Randomized, controlled trial.

Table 4. The highest level of evidence available for other biological approaches to treatment resistant OCD.

	Number of favorable studies	Number of unfavorable studies	Invasiveness	Availability	Complexity	Stage
ECT	1 OS [80]	–	Moderate	Moderate	Moderate	Fourth-line treatment, may be more effective in secondary OCD
TMS	1 RCT [88]	2 RCTs [89,92]	Reduced	Restricted	Moderate	Fourth-line treatment, different outcomes may be ascribed to different sites of stimulation, parameters and duration
DBS	2 RCT [97-99,102]	–	High	Restricted	Increased	Fifth-line treatment, may be preferred than neurosurgery due to non-invasiveness and reversibility
Neurosurgery	1 SR [107]	–	High	Restricted	Increased	Fifth-line treatment

DBS: Deep brain stimulation; ECT: Electroconvulsive therapy; OCD: Obsessive-compulsive disorder; OS: Open study; RCT: Randomized controlled trial; SR: Systematic review of an open study; TMS: Transcranial magnetic stimulation.

double-blind, placebo-controlled trial of venlafaxine in OCD failed to amass statistically significant differences between the active drug and placebo at the end of 8 weeks [48]. The interpretation of this finding is limited by the short duration of treatment and it is possible that the statistical trend favoring venlafaxine at the end of 8 weeks would reach significance if patients were treated for longer periods (e.g., 12 weeks).

3. Second-line treatments

The second-line OCD treatments were similar to first-line ones in terms of the strength of evidence, invasiveness, availability and complexity of administration. Nevertheless, these strategies were tested in drug-resistant patients with OCD (i.e., those individuals who failed to show a reduction $\leq 35\%$ [or 25% according to some authors] in the Y-BOCS, and a final CGI-improvement ≤ 2 after at least one trial with an SSRI) [11]. Although clomipramine, antipsychotics, pindolol and megadoses of an SSRI are listed as alternatives that may be employed at this treatment stage, the authors believe that the majority of the available positive studies favor the first two options.

The tricyclic antidepressant clomipramine is the most studied drug in the treatment of patients with OCD. Most predictions made by Fernandez-Córdoba and Lopez-Ibór [49] almost 40 years ago proved to be right according to well-designed studies and clinical experience [50]. For example, Fernandez-Córdoba and Lopez-Ibór have already underlined that i) the treatment of OCD required high doses of clomipramine (up to 300 mg/day) for longer than usual periods; ii) the efficacy of clomipramine was greater than that of the other treatments available at that time (independent of the presence of comorbid depression); iii) the use of this drug resulted in limited improvement of symptoms; and iv) an early worsening of symptoms usually followed the discontinuation of the drug.

According to several meta-analytic studies of double-blind controlled trials conducted in patients with OCD, the effect

size of clomipramine was greater than those associated with SSRIs [12-16], however, a few head-to-head studies show these drugs to be equivalent in terms of efficacy (e.g., 39). There are many theories to explain this apparent superiority, ranging from the greater proportion of placebo responders in recent SSRI trials compared with earlier clomipramine studies, to the particular pharmacodynamic properties of clomipramine (i.e., the noradrenaline re-uptake inhibition effect of its main metabolite, desmethylclomipramine [51], and the dopamine-blocking activity of the parent drug [52]).

Unfortunately, the authors believe that the side-effect profile that results from the anticholinergic (constipation, blurred vision, dry mouth and drowsiness), antihistaminergic (weight gain and drowsiness) and anti- α -adrenergic (dizziness and reduced blood pressure) effects of clomipramine makes it a second-line treatment, an opinion that is shared by many other consensus studies [25,29].

At least 10 double-blind, placebo-controlled studies of antipsychotic augmentation of patients with treatment-resistant OCD have been published, including studies with haloperidol, risperidone, olanzapine and quetiapine (see Table 3). Some recent meta-analytic reviews of these studies [19-21] suggest that antipsychotics may be helpful in these cases. The studies reviewed by Bloch *et al.* [19] and Skapinakis *et al.* [20] largely overlap, with the exception of the single-blind, placebo-controlled quetiapine trial conducted by Atmaca *et al.* (see Table 2) that was included only in the later review. These two meta-analyses have found evidence supporting the efficacy of risperidone and haloperidol [19,20], particularly when employed in higher doses [20] for > 8 weeks [20] in patients with tic disorders [19,20] and/or with greater degree of resistance to SRI [19,20]. Only a third of the patients with treatment-resistance OCD showed a meaningful treatment response to antipsychotic augmentation. The greater D₂ receptor-blocking properties of risperidone and haloperidol might account for the superiority of their effects.

On the other hand, Fineberg *et al.* focused their analysis on the three randomized double-blind placebo-controlled trials of quetiapine in patients with treatment-resistant OCD [21]. Although these authors argued that quetiapine was superior to placebo, they acknowledged that they could not be confident about its efficacy, as the effect of this drug edged towards the 'line of no effect' of the forest plot and overlapped with the region of uncertainty.

4. Third-line treatments

Although third-line treatments also comprised strategies with solid evidence of efficacy stemming from controlled studies, widespread availability and reduced complexity of utilization, they are either more invasive (intravenous clomipramine) or associated with other substantial risks, such as the development of abuse, tolerance or withdrawal reactions (oral morphine). Moreover, unlike first- and second-line treatment strategies, these treatment approaches are infrequently employed in the daily clinical practice, and it is unlikely that they will be incorporated in feasible treatment guidelines in the near future.

In a double-blind, placebo-controlled study, Fallon *et al.* randomized patients with clomipramine-refractory OCD to 14 daily infusions of up to 250 mg of clomipramine or placebo [53]. No infusions were performed during the weekends. Therapeutic effects were seen after week 4 of treatment: > 21% (6 of 28) of the patients treated with clomipramine responded (according to the CGI [Clinical Global Impressions scale]) as compared with 0% (0 of 23) patients treated with placebo. The effects of intravenous clomipramine were further investigated by Koran *et al.*, who randomized patients with non-treatment resistant OCD to either pulse loading (up to 200 mg/day on day 2) or gradually increasing intravenous doses of clomipramine (up to 200 mg/day on day 14) followed by oral clomipramine, until 6 months of treatment were completed [54]. Although the first group experienced a significant improvement after 6 weeks, no significant difference was noted in the long-term.

Koran *et al.* [54,56] investigated whether pulse-loaded intravenous clomipramine was more effective than pulse-loaded oral clomipramine among patients with ordinary [55], as well as treatment-resistant OCD [56]. Although the pulse-loaded intravenous clomipramine was superior to the pulse-loaded oral clomipramine in the first group, it proved to be of no further benefit than the oral strategy in the latter. Therefore, although there is some evidence that intravenous clomipramine may help in patients with treatment-resistant OCD, it seems that a pulse-loaded intravenous strategy is not significantly superior to a pulse-loaded oral one.

The same group [56] randomly assigned 23 patients with OCD resistant to at least two SRIs to random-order, 2-week blocks of once-weekly oral morphine, lorazepam and placebo. In this trial, 30% of patients responded to oral morphine, 17% to lorazepam and 0% to placebo. The authors speculated

that the therapeutic effects of morphine might be due to: i) receptor-mediated suppression of the GABAergic inhibition and consequent optimization of serotonin availability in the striatum and globus pallidus; or ii) the reduction of glutamate levels in the medial prefrontal cortex [56]. The most significant side effects included sedation, dizziness, nausea and fatigue. Although the authors did not witness euphoric effects in any of their subjects, the limited duration of the study might have prevented such complications from becoming manifest. Therefore, drugs with less abuse potential than morphine, such as methadone, a μ -agonist, and buprenorphine, a mixed agonist/antagonist at the μ -receptor, deserve further study.

5. Fourth-line treatments

Treatment at this stage included those therapeutic approaches tested only in patients with treatment-resistant OCD. Fourth-line interventions comprised: i) the less-invasive and non-complex alternatives that, despite being widely available, are not supported by controlled trials (i.e., the so-called 'heroic drug strategies'); ii) the less-invasive and moderately complex alternatives that, despite being supported by controlled trials, are not widely available (i.e., TMS); and iii) the more-invasive and moderately complex alternatives that, despite being widely available, are not supported by controlled trials (i.e., ECT). These treatments were grouped in this stage because each of them present at least one major drawback.

The drug combinations that, despite being reported to be effective in open trials, did not have their efficacy and safety systematically assessed under controlled conditions, are referred to as 'heroic drug strategies'. Although these heroic drug strategies are probably more frequently used by clinicians than the efficacy-proven intravenous clomipramine and oral morphine, they were considered fourth-line treatments because of the low quality of evidence supporting their use.

These drug combinations generally consisted of an SSRI, clomipramine or venlafaxine plus a drug with an action on another neurotransmitter system, including different dopaminergic (amisulpiride [57]), serotonergic (clomipramine [58], triptophan [59], triptans [60], fenfluramine [61], and perospirone [62]), noradrenergic (reboxetine [63]), glutamatergic (riluzole [64,65], memantine [66,67], lamotrigine [68] and topiramate [69,70]), GABAergic (valproate [71]) and nicotinic receptors (nicotine gum [72,73]), or ion channels (carbamazepine [74] and oxcarbazepine [75,76]). Monotherapy with high-dose venlafaxine, a similar strategy based on tapping an additional non-serotonergic neurotransmitter system (i.e., the noradrenergic system) was also employed successfully in open-label trials [77,78].

In a recent review, Dell'Osso *et al.* have assessed the usefulness of the administration of ECT and TMS in patients with treatment-resistant OCD [79]. They found the employment of ECT in treatment-resistant patients with OCD to be useful in 5 isolated case-reports and in a single case series of 32 patients [80]. Nevertheless, the authors have questioned the efficacy of

ECT in these patients based on: i) an 'understandable' lack of double-blind treatments; ii) the low number of patients treated; iii) the possibility of a publication bias (i.e., negative case reports would not have been published); and iv) the fact that ECT would reduce OCD symptoms by treating mental conditions comorbid with OCD (i.e., schizophrenia, depression and Tourette's syndrome).

Although the authors strongly agree on many of the above suggestions [79], there are a number of points that should also be taken into consideration. First, as OCD responds preferentially to high-dose, long-term, SRI treatment, it would be interesting to test whether patients with OCD would need higher electrical doses (e.g., supra-threshold right unilateral ECT [81]) and/or a greater number of therapeutic sessions to improve. Second, there are several additional reports of ECT being successfully employed to treat resistant OCD symptoms [82-87], including case reports of patients from countries as different as Germany [84,86], India [83] and Brazil [87]. Third, publication bias affects all types of research, including the double-blind and the placebo-controlled studies. Finally, comorbid disorders are extremely frequent in patients with treatment-refractory mental disorders, making it almost impossible to recruit a significant number of patients with 'pure' OCD to be treated with ECT or any other type of more invasive therapeutic modality (such as DBS or neurosurgery) in a research setting. The authors believe that double-blind, placebo-controlled studies of ECT in patients with OCD are urgently needed to clarify these issues.

Although much attention has been directed to the utilization of TMS in neuropsychiatric disorders, there is a significant dearth of clinical trials on this therapeutic strategy in OCD [88-92]. Moreover, their findings are inconsistent, probably because of the small number of patients enrolled and wide variation in study designs, treatment duration, stimulation site and other parameters [79].

In a recent systematic review published in 2003 [93], only two studies reported data in TMS in a suitable form for quantitative analysis [88,89]. Both studies employed stimulation to the lateral prefrontal cortex, one with high- [88] and the other with low-frequency stimulation [89]. In this review, no significant difference was seen between rTMS and sham TMS using the YBOCS or the Hamilton Depression Rating Scale scores for all time periods analysed [93]. Likewise, in the study by Prasko *et al.*, 33 right-handed patients with treatment-resistant OCD were randomly assigned to either 10 active or 10 sham sessions of low-frequency left dorso-lateral prefrontal cortex rTMS [92]. Both groups improved during the study period, but the treatment effects did not differ between them.

Two recent non-controlled trials of rTMS in treatment-resistant OCD have apparently challenged this view. In a study by Sachdev *et al.*, 4 out of 12 of patients with treatment-resistant OCD responded to daily high-frequency rTMS applied for 2 weeks; 2 patients to right and 2 to left prefrontal lobe stimulations [90]. In another open-label study, Mantovani *et al.* employed bilateral low-frequency rTMS to

the supplementary motor area of 10 patients with OCD and/or Tourette's syndrome (7 with OCD). Patients were treated from Monday to Friday, for a total of 10 days. Symptom improvement correlated with a significant increase of the right hemisphere hyperexcitability (evaluated by means of the resting motor threshold) and remained stable following a 3-month follow-up. Mantovani *et al.* suggested that the supplementary motor area might be a key target for inhibitory stimulation in OCD, given its connections with the striatum, a region implicated in the pathophysiology of OCD. Controlled studies are needed to confirm this hypothesis. Although appropriate stimulation sites, treatment duration and stimulation parameters are still controversial, these promising preliminary results, the non-invasiveness of TMS and its good tolerability support further research with this technique [79], which might be tried before procedures such as DBS or functional neurosurgery.

6. Fifth-line treatments

In DBS procedures, the electrodes are implanted into specific brain regions, and continuous electrical high-frequency stimulation is delivered via an implanted, externally programmable pulse generator, similar to a cardiac pacemaker [94]. Although this technique has been more frequently used by neurologists and neurosurgeons in the management of Parkinson's disease, dystonia, tremor and epilepsy [94-96], a handful of studies have suggested that it may also help patients with treatment-resistant psychiatric disorders, including OCD [97-103].

The mechanism of action of DBS involves a blocking effect on the stimulated area (in the case of OCD, the anterior limb of the internal capsule), an action that mimics the consequences of tissue lesioning [79]. Because DBS is reversible, adjustable, less invasive and superior to 'stimulator off-conditions' in controlled studies [97-100], it is preferable to ablative procedures [94]. A study in 2006 employed positron emission tomography during acute DBS in patients with treatment-resistant OCD found that this resulted in a significant activation of the orbitofrontal cortex, anterior cingulate cortex, striatum, globus pallidus and thalamus – a circuitry implicated in the pathophysiology of OCD [103].

The benefits that result from DBS are probably long lasting. In a study by Greenberg *et al.*, 8 out of 10 patients with treatment-resistant OCD treated with quadripolar stimulating leads implanted bilaterally in the ventral capsule/ventral striatum were followed for at least 3 years [104]. Following this, 6 patients had a decrease of $\geq 25\%$ in the YBOCS scores, and 4 patients showed a decline of $\geq 35\%$ at the final follow-up assessment.

In most patients treated with DBS, few side effects were seen. However, different unwanted symptoms are likely to occur according to the sites of stimulation. For example, effects such as taste, smell, motor smile, autonomic changes, increased breathing rate, sweating, nausea, cold sensation, heat sensation, fear and panic occurred with more ventral stimulation. Further,

higher amplitude ventral stimulation resulted in more unacceptable side effects [105].

Matthew *et al.* found that in a random sample of the members of the American Psychiatric Association, 82.8% of the psychiatrists were aware of the value of neurosurgery for the treatment of resistant OCD, and as many as 72.1% of them would indicate this procedure for the appropriate patients [106]. Despite this apparent popularity, an important question remained unsettled: when should a psychiatrist refer a patient with OCD to neurosurgery? Several studies recommend neurosurgery for individuals for whom OCD is mainly nosological entity, when the duration of illness has been at least 5 years and where significant symptomatic improvement (i.e., > 25% reductions in the baseline YBOCS) are absent after: i) treatment with at least 3 SRIs (including clomipramine) and 2 augmentation strategies in the maximum tolerated dosis for at least 12 weeks; and ii) a minimum of 20 h of CBT (cognitive behavioral therapy) [108]. As noted in the treatment algorithm in **Figure 1**, the authors would add strategies such as intravenous clomipramine, oral opioids, 'heroic drug strategies', TMS or ECT, before neurosurgery is considered.

At least five neurosurgical approaches to treatment-resistant OCD have been described in the literature, all of them involving the selective interruption of one or more parts of the cortico-striatal-thalamo-cortical circuitry [108]. These sections are made either by radiofrequency or radiosurgery, depending on the area to be lesioned. Based on a systematic review of 36 studies of neurosurgery on OCD conducted in 2004 (that excluded isolated case reports), Lopes *et al.* [107] reported the following rates of global postoperative improvement: anterior capsulotomy, 38 – 100%; anterior cingulotomy, 27 – 57%; subcaudate tractotomy, 33 – 67%; limbic leucotomy, 61 – 69%; and central lateral thalamotomy/anterior medial pallidotomy, 62.5% [107].

A critical evaluation of older studies is difficult for several reasons, including the enrollment of patients who had not undertaken modern anti-OCD treatment (SSRIs and CBT), inconsistencies in illness definition across treatment sites and, more importantly, lack of operationalization of treatment response, resistance and refractoriness. The more recently available non-blind studies may be hampered by postoperative rater partiality [108].

Only two randomized clinical trials have been performed so far [109,110], and one of them remains incomplete. Both studies included a very small number of patients, preventing any unbiased conclusions regarding the efficacy of this treatment modality [107]. A collaborative study between Brazilian and American research groups, the first randomized, double-blind, sham-controlled clinical trial for the treatment of OCD, is being conducted, using the non-invasive γ -knife technology.

According to the review by Lopes *et al.*, the most frequent adverse events include transitory seizures, weight gain, fatigue, mental slowness, apathy and irritability [107]. Patients with poor response to surgery may be at increased risk for suicide [111]. Therefore, there is an urgent need to identify potential predictors of response to neurosurgical approaches in

treatment-resistant OCD. For example, Rauch *et al.* have suggested that higher preoperative rates of metabolism at the right posterior cingulate cortex are associated with a better postoperative outcome in patients treated with anterior cingulotomy [112]. Quite interestingly, morphometric magnetic resonance imaging scans performed after anterior cingulotomy found significant volume reductions bilaterally within the caudate nucleus, but not in the amygdala, thalamus, lenticular nuclei or hippocampus [113].

7. The case for cognitive behavioral therapy

Although a detailed review of the usefulness of CBT among patients with OCD is beyond the scope of this paper, a few words on this important alternative of psychological treatment are needed. In fact, it is beyond question that CBT is as effective as SSRIs in the management of patients with OCD [18]. These views are shared by most experts, who have listed this form of treatment as one of the first choice therapeutic approaches for OCD [29]. However, only a handful of studies have evaluated the usefulness of CBT as an augmentation strategy for patients with OCD who did not respond adequately to drug treatment [114-116]. Nevertheless, their results are promising. In the most recent study on this issue, Tolin *et al.* found that CBT incorporating exposure and response prevention is helpful for patients with OCD with greater degree of treatment resistance (i.e., failure to respond to several adequate trials of multiple medications and the presence of different types of psychiatric comorbidities). In this study, 67% of patients were rated as responders after 15 CBT sessions, but only 40% maintained this status at a 6-month follow-up [116].

In an interesting report that highlights the flexibility of CBT, Anderson *et al.* described the effectiveness of this psychotherapeutic approach, coupled with pharmacotherapy, psychoeducation and social skills training, in a patient refractory to anterior cingulotomy [117]. Based on all of these studies, the authors of the present review believe that, whenever possible, CBT-naïve patients with resistant OCD should be treated with exposure and response prevention techniques. Therefore, this therapeutic tool was included as an alternative in every stage of the authors' decision tree (see **Figure 1**). There is an urgent need to conduct studies comparing pharmacological strategies and CBT in the management of patients having OCD with differing levels of treatment resistance.

8. When should the clinician move to the next stage of treatment?

It must be stressed that the exact number of failed trials required for a given patient to move onto the next treatment stage of the treatment algorithm shown in **Figure 1** is still unclear. In fact, it seems that the failure of response to one SRI does not preclude response to another one [23]. For example, in an open study, Hollander *et al.* randomly assigned 28 patients who had not responded to at least

2 previous SRI trials to venlafaxine (225 – 350 mg/day), clomipramine (125 – 225 mg/day) or citalopram (40 – 60 mg/day) for 12 weeks [118]. Here, 3 out of 8 patients responded to venlafaxine, 3 out of 11 responded to clomipramine and 1 out of 7 responded to citalopram. At least two crossover trials support these findings [119,120].

Pigott *et al.* treated 11 OCD patients with either fluoxetine or clomipramine during 10 weeks, and then switched therapy to the other drug for an additional period of 10 weeks. They found that five patients responded preferentially to clomipramine, two to fluoxetine and four to both drugs, thus indicating that individuals not responding to one drug may still respond to the other [119]. Similarly, in the study by Denys *et al.*, 43 patients who had not responded to paroxetine 60 mg/day or venlafaxine 300 mg/day were switched to the other antidepressant for 12 additional weeks. The authors found that 42% of the non-responders benefited from a crossover to the other antidepressant, and paroxetine was clearly more efficacious than venlafaxine in the treatment of patients who had not responded to a previous trial with an SRI [120].

There are reasons to insist on a greater number of first-line drug trials early in treatment derived from naturalistic studies. In a 4-year follow-up study, 66 patients with OCD were naturalistically treated with first-line drugs, including SRIs, SNRIs and some second-line strategies [121]. Overall, ~ 30% of patients who completed the first drug trial were considered treatment responders (a reduction of \geq 35% in the Y-BOCS and a final CGI of 1 or 2). The remaining non-responding patients moved to the next stage of treatment where they were treated with a different first-line drug. Approximately 30% of patients responded to this second trial. This percentage remained the same after subsequent trials in remaining non-responding patients. After 5 sequential drug trials, only 15% of the patients remained non-responders (refractory). This observation suggests that by being sufficiently persistent with first-line drugs and increasing treatment compliance, only a small fraction of patients with OCD would need to move onto more invasive treatment modalities.

9. Conclusions

There is a wealth of evidence supporting the use of SSRI as first-line treatment for OCD. Although controlled studies of venlafaxine versus active drugs have been performed and support its efficacy in OCD, placebo-controlled studies with fixed doses of this drug would be welcome in order to further strengthen the evidence favoring its role in the treatment of OCD. Mirtazapine (as an add-on strategy) seems to accelerate the response to SSRIs, but not to increase the magnitude of the response. First-line treatments may be followed by clomipramine, combination with antipsychotics or pindolol, SSRI megadoses and CBT. There is some preliminary evidence suggesting that, with the perseverant utilization of first- and second-line therapeutic strategies, and the

adoption of a sensitive approach aiming at increasing treatment compliance, only a small fraction of patients with OCD would need to move onto more invasive treatment strategies. Additional therapies include intravenous clomipramine, oral morphine, heroic drug combinations, ECT, TMS, DBS and functional neurosurgery.

10. Expert opinion

We proposed an evidence-based treatment algorithm to be employed in OCD patients with different levels of treatment resistance (Figure 1). There is some evidence suggesting that, by being persistent with more conventional anti-obsessional drugs and increasing treatment compliance, most patients with OCD would display significant clinical improvement. Unfortunately though, a large proportion of patients either continue to be significantly symptomatic or do not benefit at all from first- or even second-line augmentation drugs. Future treatment studies should focus on therapies aimed at helping these patients and increasing remission rates. These studies should also take into account the phenotypical heterogeneity of OCD [207] and try to unveil more specific therapeutic biological strategies for patients suffering from a specific subtype of OCD (i.e., tic-related OCD, early-onset OCD and gender-related OCD) or from certain symptom dimensions (such as the symmetry/ordering, hoarding, contamination/cleaning and obsessions/checking dimensions).

Unfortunately, most pharmacological strategies for patients with OCD have been derived from the treatment of patients with other psychiatric disorders, such as major depressive disorder and schizophrenia. As OCD has an undisputable independent nosological status, the time has come to build-up more specific strategies that bypass the traditional treatment with antidepressants and/or antipsychotics. Two pharmacological treatments emerging from recent advances in the knowledge of the pathophysiology of OCD are promising, and need to be tested in future studies: the use of antiglutamatergic drugs, such as riluzole [122] (based on a putative hyperglutamatergic state in OCD), and drugs that act on serotonin 5-HT_{1D} receptors [123] (based on the findings from pharmacological challenge and genetic studies) [123]. If proven to be effective, these treatments may well represent second- or third-line drugs, given the elevated costs associated with their daily administration.

As reported above, the repeated administration of 5-HT_{1D} agonists was found to be associated with a therapeutic anti-obsessive effect [123], thus suggesting that 5-HT_{1D} antagonists could be interesting therapeutic alternatives for patients with OCD. Nonetheless, it is quite likely that the simultaneous blockade of pre and postsynaptic 5-HT_{1D} receptors could dampen the effect of the drug on net 5-HT transmission. This anticipated scenario indicates that such antagonistic drugs should be selective for the terminal 5-HT autoreceptors [208]. Therefore, new anti-OCD drugs could be selective 5-HT_{1D} antagonists that prevent the negative

feedback these autoreceptors normally exert on 5-HT release [208]. A presynaptic 5-HT_{1D} antagonist would result in enhanced 5-HT release and a more rapid therapeutic action in patients with OCD.

It has also been reported that SRIs do not increase 5-HT transmission in all structures of the OCD reverberating circuitry (i.e., the cortico–striatal–thalamo–cortical loops) [208]. In contrast, antiglutamatergic drugs (e.g., riluzole [64-65], memantine [66-67] or LY354740 [207]) could work more pervasively than serotonergic drugs by acting on afferent glutamate projections to the head of the caudate nucleus and to the orbitofrontal cortex from the thalamus [208], thus correcting the more fundamental hyperglutamatergic state found in OCD. Those glutamatergic strategies need to be investigated in future double-blind trials, and may eventually prove to be even more effective than the SRI-based ones.

Other important strategies to be implemented in future studies, aiming at better delineating decision trees, such as the one we are proposing, are independent initiatives such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [301]. The STAR*D seeks to determine which subsequent treatment strategy, in what order or sequence, and in what combination(s) are both acceptable to patients and provide the best clinical results with the least side

effects. This type of study would also generate estimates of the costs and cost offsets of such care when provided to out-patients in both primary and specialty care settings.

A qualitative systematic review such as this paper has certain inherent methodological limitations that can be only be solved by means of a quantitative appraisal (e.g., a meta-analytic approach). For example, we did not systematically assess the sample sizes (and, consequently, the ‘weight’) of each study, nor did we address the issue of publication bias in the literature about the pharmacological treatment of OCD. Publication bias is the tendency on the parts of investigators, reviewers and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings [209]. One method by which publication bias can be examined quantitatively is through the use of funnel plots, which rely on the fact that larger studies are published, irrespective of their results, whereas smaller studies are only selectively published [210]. It would be interesting if data coming from these meta-analytic procedures could be incorporated into future treatment algorithms for OCD.

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